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ARTICLE

Exploring stable, sub-ambient temperatures in mechanochemistry via a diverse set of enantioselective reactions

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Recently developed capabilities for performing mechanochemistry below ambient temperatures offer an opportunity for strengthening the fundamental understanding of energetics in mechanochemical systems. We continue exploring these fundamentals by applying a unique reactor modification to reactions both new and old in mechanochemical literature, looking back in one case to explain observations made more than ten years ago. Our investigation includes Proline-catalyzed Aldol reactions; enantioselective multicomponent reactions between an aldehyde, an amine and an alkyne; and Diels Alder reactions. Results indicate that the new system allows for independent control of temperature and frequency effects, which are often conflated and can make interpretation challenging or impossible. Implications for the field of mechanochemistry are broad, and they are especially pertinent with respect to reactor and experimental design for both mechanochemical kinetic studies and reaction discovery. Furthermore, we introduce the term “mixability coefficient,” which describes the ease of interparticle mixing, which will dictate the relative frequency dependence of the reaction rate.

Introduction

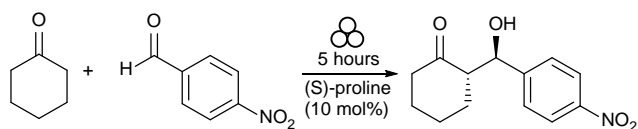
The impact of mechanochemistry is growing each year.^{1, 2} Several reviews published within the last two years alone demonstrate the applicability in all areas of synthesis: organic, organometallic, inorganic, metal-organic frameworks, and beyond.³⁻⁹ This impact often focuses on developing reactions that allow for simplified setup, work-up, and/or recycling procedures.¹⁰⁻¹⁴ Great examples of this include highly impactful cross-coupling reactions.¹⁵⁻²¹ Still others focus on altering product selectivity based on the mechanochemical environment.¹⁰ Recent advancements in high throughput milling technology will only help these discoveries occur at even faster rate.²² However, it remains necessary to continue developing a better understanding of mechanochemical systems with respect to energetics and mixing. An investment on this end may lead to profound improvements for both reactor and experimental design. In-situ monitoring techniques have proved useful for adding to the growing body of knowledge with respect to the underlying fundamentals.²³⁻²⁶ These studies and others have encouraged the mechanochemistry community to cast aside the Hot Spot Model (localized, high-energy spikes at the location of impact).²⁷⁻²⁹ Instead, energetics are now thought to be congruent with conventional, solution-based reactions. This has led to reactor modifications allowing access to stable temperatures as high as 120 °C. However, in reactions where selectivity is pertinent, it is often mandatory to perform reactions below ambient temperature. For this work, we

are defining ambient temperature to be 35 °C, as this is the typical operating temperature for a SPEX 8000M Mixer/mill operating with a cooling fan. Our recent work on this topic accessed stable milling temperatures as low as -5 °C.³⁰ The importance of temperature control has also been demonstrated on the cutting-edge technology for continuous-flow mechanochemistry, which uses a twin-screw extruder, capable of production rates of kilograms per hour.³¹⁻³³

When it comes to reporting temperatures for mechanochemical conditions, there is currently no standard. There are a variety of approaches that have been used for measuring temperatures with respect to both how and where measurements should be made. In one method, the external temperature of the vial is measured and tracked throughout the reaction.³⁴ This is often done using a coin-sized device called an iButton. K-Type thermocouples have also been fixed to this surface to record temperatures in a similar manner.³⁵ A similar method implants a thermally conductive aluminium plug into the vessel wall, allowing a temperature sensor in contact with it to track temperature.³⁶ Alternatively, the inside of the vial may be measured using an IR thermometer upon completion of reaction.^{37, 38} It is also possible to measure the temperature of the grinding media (often stainless steel balls) via calorimetry. There is not likely to be one uniform method that is appropriate for every situation or every type of mill.³⁹ The iButton may be the simplest and provide the most detail, but it may produce misleading data when there is more than one ball, when a grinding jar's filling degree is too low, or when the mill is operating at high frequency.⁴⁰ Note that all of these measurements describe a “global” or “bulk” temperature and are not concerned with attempting to measure a spike in energy associated with a hot spot. It is indeed this bulk temperature that mechanochemists should be considering.

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Scheme 1. An asymmetric mechanochemical aldol reaction catalyzed by (S)-Proline.

The above considerations have made it difficult to isolate frequency effects and temperature effects in the mill. In the past, this has made it difficult to understand the fundamental reasons why changing a given parameter may or may not have an effect on the reaction outcome. Recently, Emmerling and colleagues used in-situ monitoring via triply-coupled X-ray diffraction, Raman spectroscopy, and thermography to analyse the correlations between structural changes and temperature changes.⁴¹ Our system is unique in that temperature control and frequency control may be simultaneously possible. This allows us to add to the previous work by looking beyond correlation and start investigating causation. Stable temperatures throughout the course of a reaction might be possible because, as outlined above, our temperature control is applied to an environment in which internal temperature rises should be small. That is to say that we do not expect significant temperature changes inside the vial when we change frequency. If confirmed by data, this will allow us to investigate the variables of frequency and temperature in relative isolation from one another. Therefore, in our system we may largely consider the role of the ball and/or frequency adjustments to be limited to changes in mixing or pulverizing rather than energetic changes.

Our previous work at sub-ambient milling temperatures was limited in scope because it explored a single reaction, which has a low activation barrier while also being exothermic. Thus, while the results were illuminating, there was still much work to be done. The present work's goal is to expand the scope of that work by examining a diverse set of reactions. One component of this goal will be to repeat previous findings in the field under the temperature- and frequency-controlled conditions. With proper experimental design,

it should be possible to investigate these reactions in ways not possible before. As with the previous work, we have continued to target reactions that will occur at ambient and sub-ambient temperatures.⁴² Furthermore, we also emphasized reactions involving asymmetric synthesis. This focus was central because despite the importance of controlling selectivity, especially enantioselectivity, the knowledge regarding how to do so in mechanochemical systems remains underdeveloped, even though examples of asymmetric mechanochemical syntheses are abundant.^{3, 43, 44} Thus, with these criteria the end result of this work should impact future reactor and experimental design. This is especially the case with respect to understanding the relative roles of not only temperature control, but also maintaining properly mixed conditions inside the reactor.

Results and Discussion

Proline-Catalyzed Aldol Reactions: Temperature and Frequency

We began our investigation by exploring the first paper demonstrating enantioselective Proline-catalyzed Aldol reactions in mechanochemical conditions. This investigation was first done by Bolm and co-workers in 2006 with a follow-up paper in 2007.^{45, 46} The milling apparatus was a Fritsch Pulverisette 7, which is a planetary mill for small-scale processing. They alternated between grinding and pausing cycles, typically of 15 minutes and 5 minutes, respectively. Decreased enantioselectivities were observed with increased duty cycles, which the authors suggested in a footnote may be due to the qualitatively observed increases in reactor temperature. We chose to target their reaction between 4-nitrobenzaldehyde and cyclohexanone over a five hour reaction time, shown in Scheme 1. This produces a mixture of *syn* and *anti* products, each with a pair of enantiomers. As Figure 1 (a) demonstrates, when we applied temperature control to the milling process, we observed strict regulation of the combined yield of the diastereomers, as well the diastereomeric and enantiomeric excesses. Although the trend for selectivity is

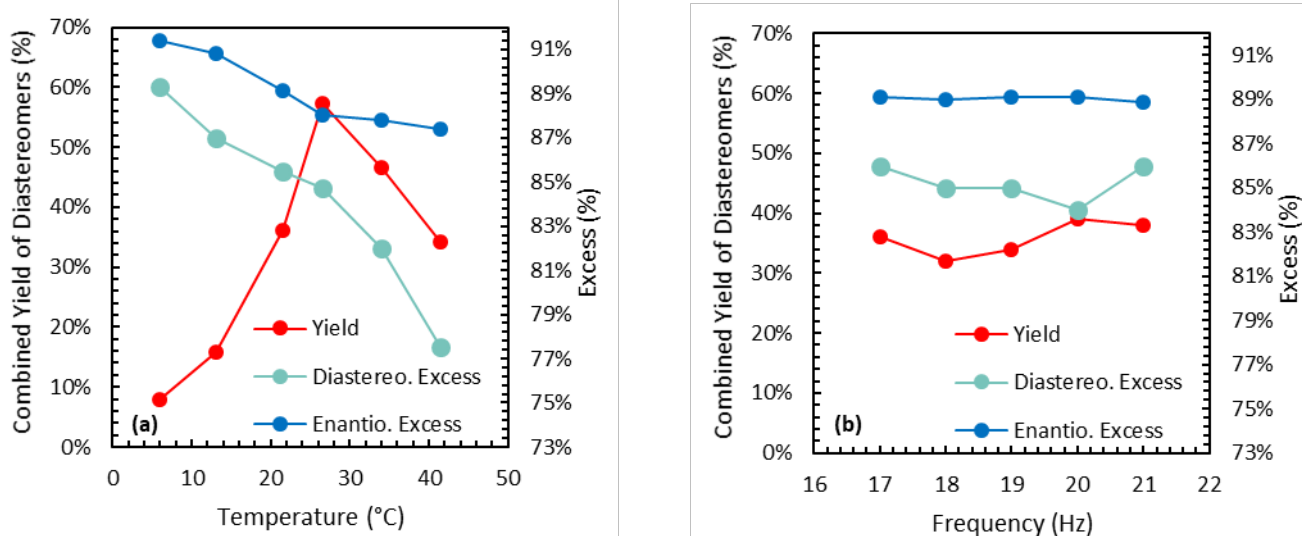


Figure 1. Isolated yields and stereoselectivities for the mechanochemical Aldol reaction as a function of (a) temperature (frequency constant at 18 Hz) and (b) frequency (temperature constant at 20 °C) during a five hour reaction. Diastereomeric excess was determined by ¹H-NMR. Enantiomeric excess was determined by chiral HPLC.

Table 1. Attempts at using additive to obtain a powdery homogeneous reaction mixture from the Proline-catalyzed Aldol reaction.^aIsolated Yield. ^bDetermined by ¹H-NMR. ^cDetermined by HPLC. ^dSee text for explanation.

Temperature (°C)	Frequency (Hz)	Additive (mg additive / mg cyclohexanone)	Combined Diastereomeric Yield (%) ^a	Diastereomeric Excess (%) ^b	Enantiomeric Excess (%) ^c	Reaction Mixture Appearance
20	18	SiO ₂ (1)	17%	74%	90.2	Paste
20	20	SiO ₂ (1)	18%	74%	89.9	Paste
26	18	SiO ₂ (1.5)	19%	65%	85.6	Powder
26	20	SiO ₂ (1.5)	17%	69%	85.4	Powder
26	18	MgSO ₄ (1.5)	37%	57%	82.7	Powder
26	18	Al ₂ O ₃ (1.5)	54%	40%	73.5	Snowball ^d
26	18	Celite (1.5)	56%	64%	88.4	Paste
26	20	Celite (1.5)	61%	63%	88.2	Paste

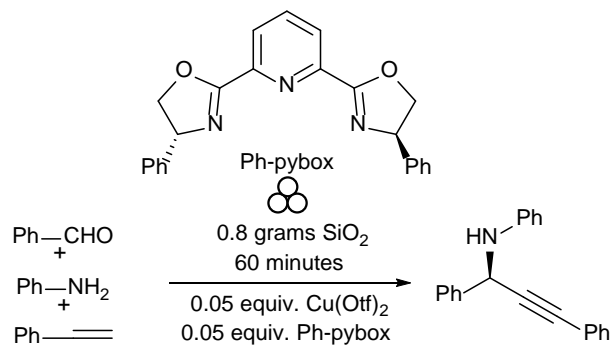
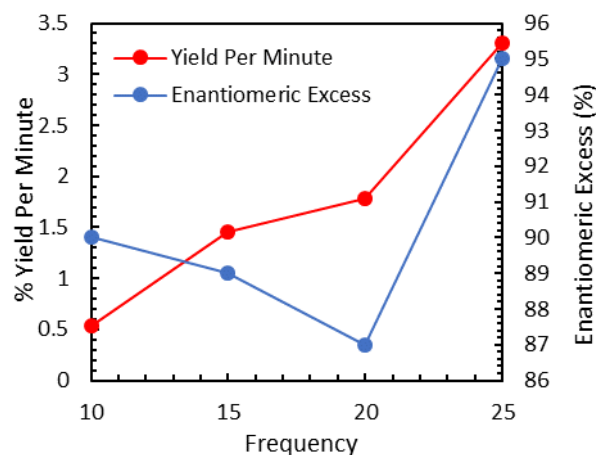
consistent across all temperatures, the combined yield of the diastereomers begins to decrease at 35 °C. This is accounted for by the appearance of undesirable, unidentified side products. In the original experiment, the temperature was constantly in flux, most likely manifesting a sinusoidal pattern over the duty cycles. However, given Bolm's results indicating near-quantitative yield, it seems reasonable to conclude that their selected duty cycle limited the amount of time during which the reaction was exposed to peak temperatures exceeding 35° C, which results in a complex mixture of products. We also found that extending the reaction time several hours at 25 °C allows quantitative conversion to the Aldol product.

We also performed a complementary set of experiments where we changed frequency while keeping temperature constant at 20 °C. Our previous work has demonstrated the stability of these temperatures from the beginning of the reaction to the end.³⁰ Numerous examples in literature have observed a strong dependence of yield on frequency.^{27, 37, 47, 48} However, as discussed earlier, we are interested in furthering the understanding of how frequency affects reactions now that

global temperature can be controlled in isolation from frequency. As seen in Figure 1 (b), we did not observe a frequency effect on yield. We attributed this to the fact that the reaction mixture appeared liquid-like in nature upon opening the reaction jar. Since a fluidic state will mix with greater ease than a solid state, it is not surprising that there was not a strong frequency dependence.

Proline-Catalyzed Aldol Reactions: Influence of Additives

In an attempt to induce a frequency dependence, we included grinding auxiliaries to produce a more free-flowing powder reaction mixture. Table 1 outlines the results of these attempts. The "snowball" term is named after its action, not its appearance. This term was coined by Boldyreva in 2016, describing the agglomeration of all reaction vessel contents into a sphere.⁴⁹ Although SiO₂ was successful in producing a powdery homogeneous reaction mixture, we still failed to observe a significant frequency dependence. Celite produced a

**Scheme 2.** Multicomponent reaction for the chiral synthesis of propargylamines as discovered by Su et al.**Figure 2.** Frequency effect on isolated yield as observed by Su et al.

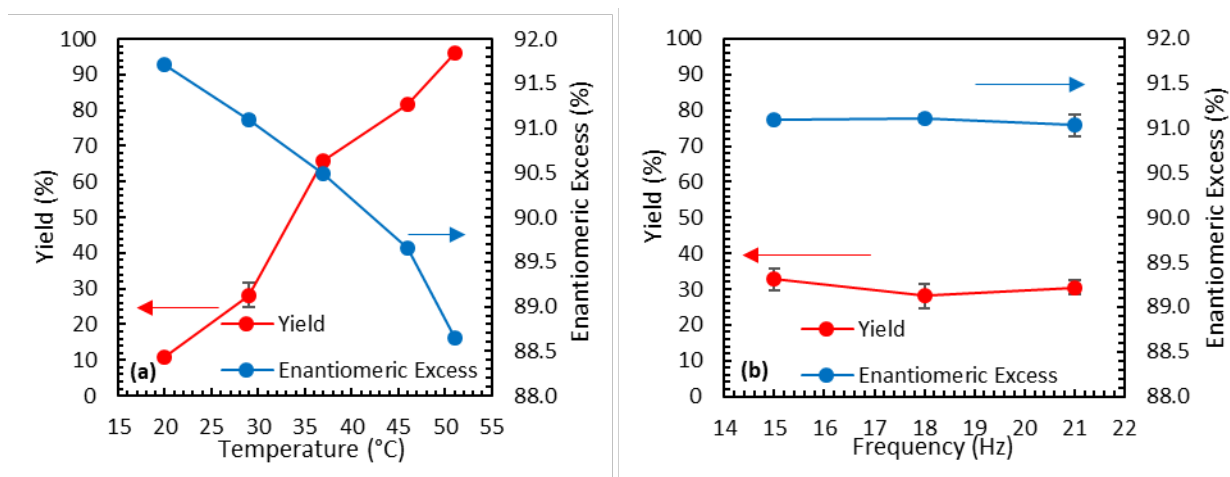


Figure 3. (a) Effect of temperature on isolated yield and selectivity at a constant frequency (18 Hz) and (b) Effect of frequency on isolated yield at a constant temperature (30 °C). %ee was determined by HPLC. To confirm lack of frequency effect in (b), these results were done in triplicate, using the standard error of the mean for the error bars. The reaction time was 30 minutes.

paste that also did not result in a detectable frequency effect. The lack of inert behaviour in several of the additives limited attempts to use MgSO_4 and Al_2O_3 . It is possible that under milling conditions, the mechanism proceeds in a manner that does not produce a frequency effect. Indeed, there have been several papers published demonstrating the intricacies of the mechanism, often indicating a strong dependence on the chemical environment.^{50, 51, 52, 53} In any event, it does not appear that a grinding auxiliary can be used in this case to induce a frequency effect. However, we identified a recent report by Su et al. that observed a frequency effect in their mechanochemical multicomponent reaction.⁴⁸ Given that their optimized conditions resulted in a reaction mixture described as a free-flowing powder, this reaction became our next target.

Multicomponent Enantioselective Synthesis of Propargylamines: Temperature and Frequency

This paper by Su outlines the coupling of an alkyne, amine, and aldehyde to enantioselectively form propargylamines, as outlined in Scheme 2. This work also received interest from Hernández et al., who used calcium carbide (CaC_2) without pre-treatment as a convenient acetylene source. In the original paper, the authors exploited several opportunities made possible by using mechanochemical conditions: 1) They used silica as their grinding auxiliary, which stream-lined work-up en route to chromatography, 2) They developed a method stable under normal air conditions for a reaction that conventionally requires air-free techniques, and 3) They designed for simplified recycling. Furthermore, and of highest significance, they observed a profound frequency effect and found the optimum condition to be the highest frequency setting. Their optimization table changes both frequency and reaction time simultaneously, which somewhat masks the frequency effect. In an effort to clarify this effect, we elected to divide their yields by the reaction times and plot the resulting yield-per-unit-time data against the corresponding frequencies (Figure 2). While it is not surprising that yield is increasing with

frequency, it is unexpected to see the inconsistent enantioselectivity trend. Although it initially decreases with increasing frequency, there is a sudden increase in selectivity at the highest frequency. Surprisingly, their discussion on the frequency results was sparse. Possibly, this is because temperature control was not available for their shaker mill, and thus it was not possible for them to separate the effects of temperature and frequency. As in the work by Bolm et al., Su's work required on-off duty cycling to minimize elevated temperatures. The precise ratio for cycling was not included. Instead, they mention opting to pause their mill after 10 minutes and only start it again when it had cooled down to room temperature (total "on" time was 30 minutes for most of their reactions). It may be the qualitative nature of this duty cycle that is responsible for the inconsistent enantioselectivity trend.

With these notes in minds, we applied our temperature-controlled mill to their reaction. Specifically, we targeted the reaction that demonstrated the lowest stereoselectivity in their substrate scope. For that work, this involved the coupling of 4-nitrobenzaldehyde, aniline, and phenyl acetylene, resulting in a yield of 99% with an enantiomeric excess of 83%. Although two of the reagents are liquids, the grinding auxiliary produces a fine powder on which the reactants are distributed. Upon running the reaction at specified, stable temperatures, we saw a straightforward effect for both yield and enantiomeric excess, as Figure 3(a) shows. For this reaction, unlike the previously discussed Aldol reaction, we do not observe the appearance of side products at higher temperatures. However, temperature's negative impact on enantioselectivity limits one from simply performing this reaction at elevated temperatures to increase reaction rate. Interestingly, even at our highest tested temperature (50 °C), we observed higher enantiomeric excess than the original paper. With the caveat that the mills used were not the same (nor the reagent suppliers), this may suggest that temperatures exceeding 50 °C were quickly reached (< 10 minutes) in their mill.

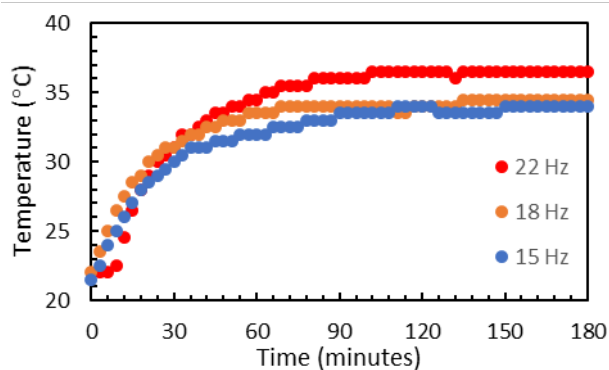


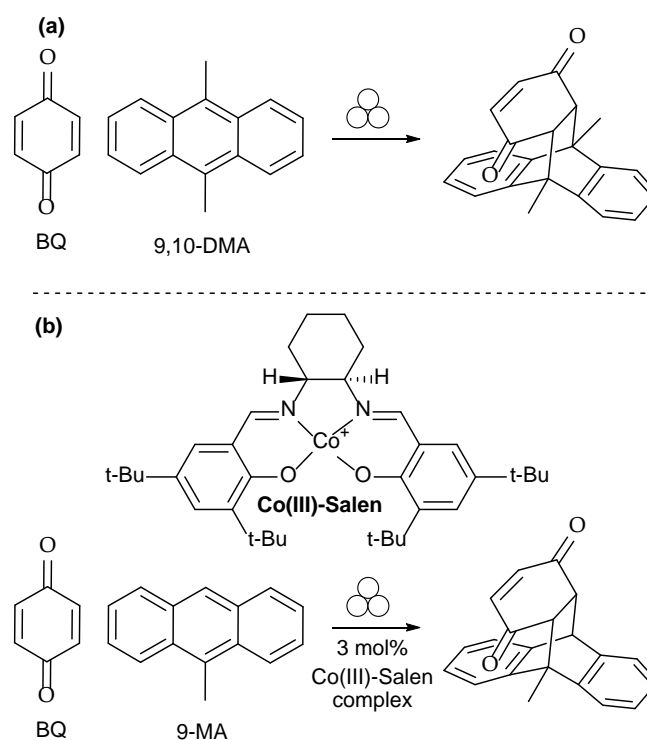
Figure 4. Heating rates at different frequencies in the absence of externally applied temperature control.

Having obtained an idea of the energetic sensitivity of both the reaction rate and the selectivity, we next altered frequency while maintaining a constant 30 °C global temperature of our reaction jar. These results are presented in Figure 3 (b). Note that the range of frequencies used by Su are different from what are used in our mill. The respective ranges are related to the brand and model of the mill. Since the nature of motion and operating temperature is different between each mill, results at identical frequencies shouldn't be compared. The typical operating frequency of our SPEX 8000M Mixer/mill is 18 Hz, and we have previously observed exponential effects on yield while varying the frequency between 15 and 22 Hz.²⁷ We were surprised to see their frequency effect disappear upon incorporating temperature control. Of note is that in addition to the yield being unaffected, the enantiomeric excess is also unaffected by frequency. However, Figure 3 (a) demonstrates that even slightly changing the temperature from 30 °C to 35 °C resulted in significant rate enhancements and a decrease in enantiomeric excess. Thus, we conclude that the cooling of the vial was sufficient to counteract any increases in internal frictional heating of the vial due to more intense ball-wall collisions at higher frequencies. This is reasonable under our conditions because all the reactions that we performed contained a single ball inside the reaction jar. Furthermore, the large amount of pulverized, powdery silica may act as a shock absorber to decrease frictional heating. This lack of frictional heating seems less likely to hold true for planetary mills or shaker mills when operating with many balls. Indeed, since they included more than one ball in their reactor and lacked temperature control, the observed rate enhancements were likely due to elevated temperatures, with increased mixing have a negligible effect. Furthermore, given the straightforward behaviour of selectivity in our system, it seems likely that the sudden increase of enantioselectivity at their highest frequency was not a direct result of the frequency. Perhaps it was a result of the qualitative nature of the duty cycling (which indirectly affects the temperature of their system). Outside of this data point, their enantioselectivity trend is readily explained in the same manner as the yield trend is explained (i.e., increases in the global/bulk temperature of the milling vessel).

Multicomponent Enantioselective Synthesis of Propargylamines: Silica and the Lack of an Observed Frequency Effect

To justify the lack of a frequency effect in our experiments, reflecting on mixing behaviors in mills is helpful. Although the silica allows the reaction mixture to be a free-flowing powder, it also acts as a support, greatly spreading out both the reactants and products. This vastly increases the exposed surface areas of the reaction's components. In contrast, for the case of our 2017 Diels Alder work, all reaction material is crowded on the walls of the vial.²⁷ In that case, exposed surface areas of reactants would be much lower and harsher mixing conditions (higher frequencies) may be mandatory to see a frequency effect. With this in mind, it is reasonable that increasing the milling frequency over our targeted range does not notably affect the reaction rate for the A³ reaction. This may also apply to the Proline reaction above when the additives were included. We see this as evidence that any given system of reactants, intermediates, products, and additives will have a certain "mixability coefficient." This term describes the ease with which interparticle mixing occurs, impacting the extent of a frequency effect. For some reactions, this coefficient may change drastically during the course of a chemical reaction. This coefficient is further discussed below in the context of rheology.

Diels Alder Reactions and the Role of Rheology in Frequency Effects



Scheme 3. Mechanochemical Diels Alder reactions occurring (a) racemically in the absence of a catalyst between benzoquinone (BQ) and 9,10-dimethylantracene (9,10-DMA) and (b) Between BQ and 9-methylantracene (9-MA) in the presence of a chiral Co(III)-Salen complex.

We now find it pertinent to explore Diels Alder reactions, because in 2017 we reported exponential frequency effects in the reaction between benzoquinone (BQ) and 9,10-dimethylantracene (9,10-DMA), outlined in Scheme 3(a). The yield of that reaction increased from 14.2% to 92% when frequency varied from 15 to 21. Doubling of yield was observed every 2 Hz increment and required no grinding auxiliary. In that

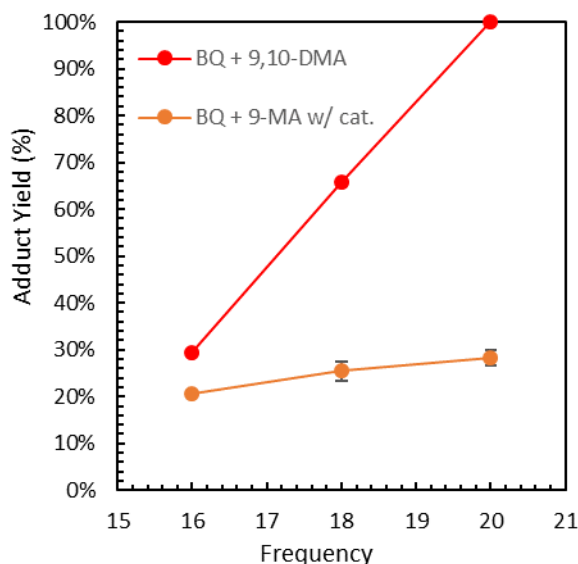


Figure 5. Frequency effect on the isolated yield for two different Diels-Alder reactions under mechanochemical conditions. The reaction time was three hours. Error bars for BQ + 9,10-DMA are calculated as standard error of the mean ($n=3$).

work, temperature was monitored, but not controlled, during the course of the three-hour reaction. Over the entire range of frequencies, our monitored temperature only changed by 2.5 °C. Moreover, as demonstrated by Figure 4 (previously unpublished) the heating rates remained consistent. We began by reproducing the frequency effect for BQ and 9,10-DMA now that we have proper temperature control. As Figure 5 shows, the trend observed previously persists throughout our tested range. The yield is higher than in the previous work because the temperature-controlled system is pre-equilibrated prior to $t=0$, so the new system has a much shorter warm-up period as compared to what is seen in Figure 4 for the old system. Thus, we have confirmed our previous example of an exponential frequency effect in a temperature-controlled system.

We next used the reaction outlined in Scheme 3(b) for comparison, because it would have an identical mechanism, but will have reactants with different physical properties including mixing characteristics. Literature has shown Salen-Co (III) complexes to induce enantioselectivity in Diels Alder reactions.^{54,55} In a control experiment, performing the reaction in the absence of a catalyst produced no observable yield at 25 °C. Upon running this reaction at the intermediate frequency of 18 Hz with 3 mol% catalyst loading at 25 °C, we achieved approximately 30% yield.⁵⁶ Unfortunately, due to limitations in the work-up and separation (See Supporting Information), we struggled to obtain HPLC samples capable of producing reliable

enantioselectivities. However, since the yield results are sufficiently illustrative, we have reported that data without the including the selectivity results. Strikingly, when we controlled for temperature while running the reaction at various frequencies (Figure 5), we observed only a very minor—perhaps negligible—frequency effect. The frequency effect is undeniably stronger for the reaction between 9,10-DMA and BQ.

At this point, it becomes important to consider the rheology of the system. The conversation regarding rheology, which deals with the deformation and flow of matter in a system, in mechanochemical organic reactions was formally opened in 2017 by the James group.³⁸ Certainly, reaction mixtures that flow and mix most readily (e.g., those containing only co-soluble liquids) will be minimally affected by changes in frequency when compared to mixtures containing solids. However, even when the mixture can be characterized as a solid, there exists a spectrum of how easily the solid can be mixed.⁵⁷ It is worth noting that both systems described in Figure 5 enter and exit the mill as solids. Thus, Figure 5 provides evidence that when considering frequency as a tool for influencing reaction rate, careful attention to the rheological characteristics and/or the presence of a grinding auxiliary must be made. Future rheological studies in temperature-controlled mechanochemical systems are suggested to better understand the interplay between reaction rate and rheological properties.

Conclusions

In this study we have explored the effects of temperature and frequency in mechanochemical systems by controlling them in isolation from one another. This is made possible both by the choice of mill (mixer mill, one ball) as well as the modifications made to allow frequency control and temperature control. Evidence for the isolation of the two variables is given by the lack of change in yield and enantioselectivity of a diverse set of reactions when frequency is changed at constant temperatures. In contrast, temperature-altering experiments indicated that temperature changes as minor as 5 °C can affect both yield and enantioselectivity. With respect to the relationship between the operating frequency and the efficient mixing of reactants, we propose the term “mixability coefficient” to describe the ease or difficulty of interparticle mixing. Easily mixed systems will not be much affected by frequency changes, whereas systems that are difficult to mix may achieve significant rate enhancements by increases in frequency. This mixability coefficient is likely a function of both the rheological properties of the reactants and reagents, as well as the use of a grinding auxiliary. The presence of a grinding auxiliary may decrease the significance of the mixability coefficient by increasing the surface area available to the reaction mixture. Table 2 provides some details on which experiments provided which conclusions, and compares with the original works.

For chemists attempting to optimize mechanochemical reactions, it is key to properly identify whether the system is limited by its mixing or its temperature. Mixing problems can

Table 2. Summary of the findings/observations of the original works and the current work.

Topic	Original Work	Current Work
Proline-Catalyzed Aldol	High operating frequencies, or extended milling without pauses leads to a decrease in selectivity. A planetary mill was used, which often results in build-up of internal heat during operation.	At constant temperature, frequency changes did not impact yield or selectivity. Lack of a frequency effect on rate was attributed to 1) No heat build-up and 2) A liquid-like reaction mixture that is easily mixed even at low frequencies. Attempts to induce a frequency effect by providing an grinding did not succeed because a sufficiently inert agent was not found.
A ³ Click Reaction	Operating frequency strongly influenced reaction rate and was generally correlated to a decrease in enantioselectivity. Reaction was performed using silica as a grinding auxiliary. Milling was performed in a shaker mill using more than one ball.	At constant temperature, frequency changes did not impact yield or selectivity despite the reaction mixture's powdery appearance. We suggest that the grinding auxiliary (silica) increases the exposed surface area of the reactants so immensely that the mixing rate is not impacted by changes in frequency. Additionally, since slight temperature changes caused noticeable yield/selectivity changes, we can rule out internal vial temperature changes resulting from frequency changes.
Diels Alder	Reaction of 9,10-DMA + BQ exhibited a strong frequency effect on yield at stable temperatures. Low temperature control was not possible. Temperature was tracked but not controlled. The temperature was found to be within a couple degrees Celsius when frequency was changed. Milling was performed in a shaker mill with a single ball.	We confirmed the exponential frequency effect in presence of our new temperature control. However, a similar Diels Alder reaction between BQ + 9-MA with a catalyst produced a minor/negligible frequency effect. As the most relevant consideration is the relative physical characteristics of the materials, the present story joins up with James' discussion on the importance of rheology in milled processes.

potentially be solved by application of the proper grinding auxiliary, if a suitable one can be found. If the problem does not appear to be one of mixing, and selectivity is not a concern, then it is suggested to obtain higher temperatures, ideally by means of external temperature control. In the absence of external temperature control, as it is not yet commercially available, one may try to achieve higher temperatures by favoring multiple smaller balls as opposed to one larger one and/or using higher operating frequencies. On the other hand, if the reaction rate is satisfactory, but the selectivity is poor, then lower temperatures should be targeted. This can be approached using low-temperature milling. If that is not possible, then using fewer balls or lower operating frequencies may help. Expanded availability of temperature-controlled mills and an improved understanding of the grinding auxiliary selection process will greatly benefit the optimization process.

Conflicts of interest

The authors are in the process of patenting the chilling mechanism for the SPEX 8000M Mixer/mill, although some details are provided in Ref. 30.

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56. In a control experiment. performing the reaction between 9,10-DMA and BQ in the presence of the cobalt catalyst at 18 Hz increased the yield from 65% to 100%.
57. In our previous Diels-Alder work, we investigated what happens when a reaction (anthracene + BQ) is heated without simultaneous milling. With combined milling and heating at 100 °C, quantitative yield is reached in three hours. When milled for three hours without heating (0% yield) followed by heating for three hours with no motion, we obtain 19% yield. These experiments indicated to us that although the reaction can occur without the ball, the rate is limited in a manner similar to an un-stirred solution reaction.